REMARKS

Claims 1, 2, 4-7, 9-17, 20-23, and 43-47, are pending and under examination in the subject application. Applicants have hereinabove canceled without disclaimer or prejudice claims 15, 21 and 22 and amended claims 1, 2, 13, and 16. Support for the amendment of claim 1 may be found in the specification inter alia at page 31, lines 20-34 and page 34, line 32. Support for the amendment of claim 2 may be found in the specification inter alia at page 29, line 11-14 and page 34, line 32. Support for the amendment of claim 10 may be found in the specification inter alia at page 32, line 1-3. The amendment of claim 13 corrects a grammatical error by deleting "are" and inserting "is". Support for the amendment of claim 16 may be found in the specification inter alia at page 33, lines 4-6 and 15-16. Applicants maintain that the amendments to the claims are supported by the specification, and thus raise no issue of new matter. Accordingly, applicants respectfully request that the Examiner enter the Amendment. Upon entry of the amendment, claims 1, 2, 4-7, 9-14, 16-17, 20, 23, and 43-47, as amended, will be pending and under examination in the subject application.

NEW REJECTION

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner asserted that claims 15-17 are allegedly indefinite

because claims 15 and 16 recite the language "a biologically active substance" and it is not clear what kind of activity is referred to.

In response, but without conceding the correctness of the Examiner's position, applicants have hereinabove canceled without disclaimer or prejudice claim 15 and amended claim 16 to recite: "...wherein the viable cells comprise endocrine cells." Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above-stated rejection of claim 16.

The Examiner rejected claims 1-2, 4-7, 9-17, 20-23, 43-47 under 35 U.S.C. §112, second paragraph, because claim 1 is incomplete, omitting essential steps, such omission amounting to a gap between the steps (citing MPEP § 2172.01) and asserted that the omitted steps are: 1) Administration of the cells, and 2) A step correlating back to the preamble.

In response, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 1 to recite step (b): "transplanting the viable cells or tissue comprising the viable cells contained in the semipermeable membrane, obtained in step (a) into the subject;" and have added to step (c) "thereby inhibiting viable cells or tissue comprising the viable cells transplanted into the subject from being destroyed by the subject's immune system.", which correlates back to the preamble (Emphasis added) Accordingly, applicants respectfully

request that the Examiner reconsider and withdraw the above-stated rejection of claim 1 and claims dependent thereon, i.e. claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47.

The Examiner asserted that claims 1-2, 4-7, 9-17, 20-23, and 43-47 are indefinite because in claim 1, it is not clear whether the "device" is administered.

In response, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 1 to recite step (b): "transplanting the viable cells or tissue comprising the viable cells contained in the semipermeable membrane, obtained in step (a) into the subject;". (Emphasis added) Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above-stated rejection of claim 1 and claims dependent thereon, i.e. claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47.

The Examiner asserted that claims 10 and 11 are indefinite, because claim 10 does not further limit claim 9, from which claim 10 depends.

In response, but without conceding the correctness of the Examiner's, applicants have amended claim 10 to depend on claim 1. Accordingly, claims 10 and 11 further delineate "the viable cells or tissue comprising the viable cells" of claim 1 through their dependency on claim 1.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above-stated rejections under 35 U.S.C. § 112, second paragraph.

NEW REJECTION

Rejection under 35 U.S.C. §112, First Paragraph, Scope

The Examiner rejected claims 1-2, 4-7, 9-17, 20-23, and 43-47 under 35 U.S.C. §112, first paragraph, because the specification, while allegedly being enabling for a method for inhibiting graft rejection, comprising containing the viable cells or tissues in a device comprising a semipermeable membrane prior to transplantation, and treating a subject transplanted with said cells MR1, or CTLA4, or CTLA4Ig, does not reasonably provide enablement for a method for inhibiting graft rejection, comprising containing the viable cells or tissues in a device comprising a semipermeable membrane prior to transplantation, and treating a subject transplanted with said cells a substance which inhibits an immune system costimulation event. (Applicants' emphasis added - no data on "CTLA4 in specification") The Examiner asserted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Examiner stated that claims 1-2, 4-7, 9-17, 20-23, and 43-47 are drawn to a method for inhibiting graft rejection, comprising containing the viable cells or tissues in a device comprising a

semipermeable membrane prior to transplantation, and treating a subject transplanted with said cells a substance which inhibits an immune system costimulation event. The Examiner stated that the specification discloses that a substance, which inhibits an immune system costimulation event, includes, but not limited to, T cell or APC cell surface-molecule analogs (p.27) and that the specification and the claims encompass a variety of compounds, a substantial number of said compounds would not inhibit an immune system costimulation event.

The Examiner stated that the term "analogs" encompass a variety of definitions, i.e. chemical modification, deletions, truncations, substitutions, conjugation, etc. and asserted that applicants have not enabled these types of modified T cell or APC cell surface molecules in the specification.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology and enumerated examples of a single amino acid substitution affecting the biological activity and characteristic of a protein.

The Examiner also stated that not any T cell or APC cell surface molecule is involved in interaction between an APC and a T-cell required in conjunction with the binding of an MHC-bound antigen on the surface of the APC to the T cell receptor, e.g. CD2, CD5 or CD7 which are lineage-specific markers (citing Stites, DP et al., eds, 1997, Medical Immunology).

The Examiner asserted that in view of the above unpredictability, and in the absence of a method of how to make a substance which inhibits an immune-response event, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In response, applicants respectfully traverse the Examiner's rejection and maintain that and the subject specification provides adequate guidance to one of skill in the art to practice the invention of presently pending claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47 without undue experimentation.

The claimed invention is: "a method of inhibiting viable cells or tissue comprising the viable cells transplanted into a subject from being destroyed by the subject's immune system which comprises: (a) containing the viable cells or tissue comprising the viable cells, prior to transplantation within a device comprising a semipermeable membrane; (b) transplanting the viable cells or tissue comprising the viable cells contained in the semipermeable membrane, obtained in step (a) into the subject; and (c) treating the subject of step (b) with a substance which inhibits an immune-system costimulation event in an amount effective to inhibit the subject's immune system from responding to said contained viable cells or tissue comprising the viable cells, thereby inhibiting viable cells or tissue comprising the viable cells transplanted into the subject from being destroyed by the subject's immune system." (emphasis added)

Therefore, any substance which does not inhibit an immune system costimulation event is not administered according to the claimed method.

Applicants respectfully note that the specification at page 27, lines 15-18, adequately provides guidance to one of skill in the art as to "a substance which inhibits an immune-system costimulation event" since "an immune-system costimulation event" is defined as an interaction between an antigen presenting cell (APC) and a T-cell in conjunction with the binding of an MHC-bound antigen on the surface of the APC to the T cell receptor. The specification, at page 27, lines 20-28, further states that immune-system costimulation events include any specific binding of an APC cell-surface molecule (other than an MHC-bound antigen) to a specific ligand on a T cell. Examples of such specific binding are provided as including, but not limited to, binding of a B7 molecule to a CTLA4 receptor or a CD28 receptor on the surface of a T cell and binding of a CD40 molecule (on the surface of an APC) to GP39 (on the surface of a T cell).

The specification further provides an example of a substance which inhibits an immune-system costimulation event: MR1, a monoclonal hamster anti-murine GP39 antibody, which blocks helper T-cell interactions with APCs, by blocking the binding of CD40 expressed on the surface of an APC to GP39 expressed on the surface of a T cell.

The specification provides another example of a substance which inhibits an immune-system costimulation event, CTLA4Ig, **not** CTLA4, which as stated on page 29, lines 11-14, alters the cytokine profile of a subject, i.e. the type and quantity of cytokine produced in a subject. CTLA4Ig, is a recombinant soluble fusion protein, combining the extracellular binding domain of CTLA4 (a cell surface protein related to C28) with the constant region of the IgG_1, which, so as to protect contained cells or tissue grafted into the subject.

The subject specification provides experimental data on CTLA4Ig administration in spontaneously-diabetic recipients, i.e. nonobese diabetic (NOD) recipients, prolonging survival of encapsulated xenograft islets (see inter alia page 57, lines 8-12, Table 6 at page 58 and Figure 21).

A third example of a substance which inhibits an immune-system costimulation event, monoclonal antibody GK 1.5, is provided in the specification on page 51, lines 1-5, which states that inhibition of CD4+ helper T cells by administration of the antibody to NOD recipients resulted in significantly increased survival of encapsulated islets.

Therefore, the subject specification provides examples of differing types of substances which may be used inhibit an immune system costimulation event. Accordingly, applicants have successfully demonstrated in the subject specification a method of inhibiting

viable cells or tissue comprising the viable cells transplanted into a subject from being destroyed by the subject's immune system which comprises encapsulation and administration of a substance which inhibits an immune-system costimulation event, therefore, the claimed method should not be limited to the exemplified substances used in such method.

Accordingly, applicants maintain that the subject specification provides adequate guidance to one of skill to practice the claimed invention without undue experimentation. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above-stated rejection of claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47 under 35 U.S.C. §112, first paragraph.

Rejection under 35 U.S.C. §103

The Examiner rejected claims 1-2, 4-7, 9-17, 20-23, 43-47 under 35 U.S.C. §103 of pertaining to obviousness over Lenschow, DJ et al., in view of Goosen et al., Soon-Shiong P et al., Akalin, E. et al., Linsley, P.S., et al., Padrid P.A. et al., and Steurer, W. et al. remains for reasons already of record in paper No. 7.

The Examiner stated: "applicant argues that none of the references suggest or teach a combination of containing the viable cells or tissues in a device comprising a semipermeable membrane prior to transplantation, and treating a subject transplanted with said cells a substance which inhibits an immune system costimulation

event. There is no suggestion that an increase in prevention of graft rejection would result when combining encapsulation with CTLA4Ig treatment. There is no reasonable expectation that combining Lenschow et al with Goosen et al will result in success. Moreover, the reference by Padrid et al should be removed because said reference discloses CTLA4Ig treatment in an animal model of asthma, and there is no connection between the asthma model and transplantation. Furthermore, the statement by the Examiner that 'Prevention of graft rejection, but by a different mechanisms, thus by logical reasoning, would increase the chance of preventing graft rejection by the immune system' does not appear to be supported by the combination of teachings of the cited art or by some specific understanding or technological principle within the knowledge of one of ordinary skill in the art."

The Examiner considered applicant's arguments but did not deem them to be persuasive and cited *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) as stating that "It is prima facie obvious to **combine two compositions each of which is taught by prior art to be useful for same purpose** in order **to form third composition** that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art." (Applicants' emphasis)

The Examiner stated that neither Lenschow et al. nor Goosen et al. teach a process for inhibiting rejection of transplanted cells by combining encapsulation of transplanted cells with CTLA4Ig

treatment. (Applicants' emphasis) The Examiner stated that "in the absence of unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to inhibit rejection of transplanted cells by combining CTLA4Ig treatment and encapsulation of cells used for transplantation." The Examiner stated that each of the methods of preventing graft rejection had been taught by the prior art.

The Examiner stated that applicants assert that the claimed methods are not obvious in view of the cited references because the cited prior art does not suggest such a combination. The Examiner asserted that the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. The Examiner applied the same logic to the instant process claims, stating "given the teaching of the prior art of processes inhibiting graft rejection by treating with CTLA4Ig and by encapsulation of cells used for transplantation, it would have been obvious to inhibit graft rejection by using both techniques of graft rejection, i.e. CTLA4Ig treatment and encapsulation of cells to be used in transplantation, because the idea of doing so would have logically followed from their having

been individually taught in the prior art to be useful as methods of inhibiting graft rejection. By logical reasoning, combining two methods of inhibiting graft rejection, each method works by a different mechanism, would increase the chance of preventing graft rejection. One of ordinary skill in the art would have reasonably expected to be successful in inhibiting graft rejection, by combining CTLA4Ig treatment and encapsulation of cells to be used in transplantation, because the methods of CTLA4Ig treatment and encapsulation of cells for use in transplantation have been taught by prior art, and both methods have been successful in inhibiting graft rejection. The citation of Padrid et al. is proper, because Padrid et al. teach an inherent property of CTLA4Ig treatment, i.e. increasing interferon-gamma."

In response, applicants respectfully traverse the Examiner's rejection of claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47 and maintain that these claims are not prima facie obvious over Lenschow, DJ et al., in view of Goosen et al., Soon-Shiong P et al., Akalin, E. et al., Linsley, P.S., et al., Padrid P.A. et al., and Steurer, W. et al. under 35 U.S.C. 103(a).

To establish a prima facie case of obviousness, the Examiner must show that, inter alia, the prior art reference (or references when combined) teaches or suggests all the claim limitations. see M.P.E.P. 2143.

Moreover, applicants maintain that the subject invention does **not** relate to combining two compositions useful for the same purpose to form a third composition useful for the same purpose. The methods of CTLA4Ig treatment and encapsulation of cells are not used for the same purpose. As stated in the specification on page 44, lines 13-18, a major function of microencapsulation is to prevent host sensitization, rather than to protect grafts from the effector arm of the response (e.g. immunoglobulins or complement effects).

The experiments of the subject specification demonstrate, as discussed on page 51, lines 5-8, that treatment of NOD mice with CTLA4Ig significantly prolonged encapsulated rabbit islet survival, from 20 ± 2 days to 98 ± 25 days ($p<.05$)(see also Table 2 and Figures 7 and 8). Accordingly, the combination of CTLA4Ig and encapsulation provides unexpected results, since as stated on page 53, lines 24-24 and Table 5 at page 55, treatment with CTLA4Ig prolonged microencapsulated donor rabbit islet xenografts, in spontaneously diabetic NODs, **when compared to either islet microencapsulation or host CTLA4Ig treatment alone**. (Applicants' emphasis)

Accordingly, the combination of cited publications which disclose microencapsulation alone or an immunosuppressive drug alone, also does not provide one of skill in the art with the suggestion to combine the respective teachings and a reasonable expectation of

success thereof.

As stated on page 11, lines 20-22, prior to applicants' experiments, "there are no report of effects of CTLA4Ig on islet survival in spontaneously diabetic recipients, such as NOD mice". As pointed out in the subject specification, on page 6, first paragraph, the NOD model is the most appropriate model for studying the feasibility of islet xenotransplantation because their disease resembles human insulin-dependent diabetes mellitus (IDDM) in several ways. Applicants note that Lenschow et al. used SZN-diabetic mice, a chemically induced model of diabetes. Accordingly, applicants maintain that results in the SZN-diabetic model do not render obvious results in a NOD model, which is a more difficult model.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above-stated rejection of claims 1-2, 4-7, 9-14, 16-17, 20, 23, and 43-47 under 35 U.S.C. § 103(a).

In summary, in view of the amendments and remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the rejections in the July 13, 2000 Office Action, and earnestly solicit allowance of the claims now pending in the subject application.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Applicants submit herewith a Supplemental Information Disclosure Statement under 37 C.F.R. §1.56 and §1.97(c). This Supplemental Information Disclosure Statement is being filed pursuant to 37 C.F.R. § 1.97(c) after the mailing date of an Office Action, but before a final Office Action or a Notice of Allowance. A non-final Office Action was issued in connection with the subject application on July 13, 2000.

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following ddisclosures, which are listed on Form PTO-1449 **(Exhibit A)**:

1. U.S. Patent No. 5,334,640, Desai et al., August 2, 1994. **(Exhibit 1)**

2. U.S. Patent No. 4,696,286, Cochrum, September 29, 1987. **(Exhibit 2)**

3. Dupuy, B., et al. (1991) "Microencapsulation of isolated pituitary cells by polyacrylamide microlatex coagulation on agarose beads", Biomaterials, 12(5):493-496. **(Exhibit 3)**

4. Hakim, F.T., et al. (1995) "Acute Graft-Versus-Host Reaction can be Aborted by Blockade of Costimulatory Molecules", J. Immunol., 155(4):1757-1766. **(Exhibit 4)**

5. Steurer, W., et al. (1995) "Ex Vivo Coating of Islet Cell Allografts with Murine CTLA4/Fc Promotes Graft Tolerance", J. Immunol., 155(3): 1165-1174. **(Exhibit 5)**

Each of the above-listed references is listed again on the accompanying Form PTO-1449 as **Exhibit A**, and copies of references 1-5 are attached hereto as **Exhibits 1-5**, respectively.

The subject application is a continuation-in-part of PCT International Application No. PCT/US96/15577, filed September 27, 1996, which is claims priority of U.S. Provisional Application No. 60/004,375, filed September 27, 1995.

Publications 1-5 were cited in a Supplementary European Search Report by the European Patent Office issued November 7, 2000 in connection with related copending European Patent Application No. 96 93 6037.9 which is a counterpart foreign application of the subject application and which is a regional stage of PCT International PCT/US96/15577. A copy of the Supplementary European Search Report for European Patent Application No. 96 93 6037.9, is attached hereto as **Exhibit B**.

Under 37 C.F.R. §1.97(c) an information disclosure statement shall be considered by the Office if filed by the applicant after the period specified in paragraph (b) of this section provided that the information disclosure statement is filed before the mailing date

of either a final action under § 1.113, or a notice of allowance under § 1.113, whichever occurs first, and is accompanied by either: (1) [a] statement as specified in paragraph (e) of this section; or (2) the fee set forth in §1.17(p).

Accordingly, this Supplemental Information Disclosure Statement is being filed before the mailing date of either a final action under § 1.113, or a notice of allowance under § 1.113.

Pursuant to 37 C.F.R. §1.97(e)(1), applicants hereby certify that each item of information contained in the Supplemental Information Disclosure Statement filed herewith, i.e. references 1-5, was first cited in a communication in a counterpart foreign application not more than three months prior to the filing of the Supplemental Information Disclosure Statement.

Applicants request that the Examiner review the publications and make them of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $445.00 for a three-month extension of time, is deemed necessary in connection with this Amendment and Supplemental Information Disclosure Statement. However, if any

additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

1/16/01

John P. White
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Date

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